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Appendices

Exclusion Criteria

We excluded 1) small case series less than ten patients, 2) case-control studies where the event rate could not be extracted from the manuscript, 3) fractures of the pelvis, hand, ribs, spine, or head, 4) studies that failed to report the timing of irrigation and debridement and were unresponsive to email requests, 5) data from systematic or narrative reviews, 6) studies that included >30% closed fractures without stratification, and 7) animal studies. It was our preference that the studies included the Gustilo or another validated open fracture classification; however, this was not mandatory.

Search Details

We used the following search terms: (“Open fracture” OR “Fracture” OR “Injury” OR “Lower Limb” OR “Upper limb” OR “Lower Extremity” OR “Upper extremity”) AND (“Debridement” OR “Irrigation” OR “Irrigation and debridement” OR “Surgery” OR “Intervention” OR “Time to surgery” OR “Time to procedure” AND “Infection” OR “Deep infection” OR “Outcome” OR “Complications” OR “Adverse” OR “Negative” OR “Deep”). We searched with Medical Subject Headings (MeSH) and text words related to open fractures, irrigation and debridement, and

infection. For each database, the syntax was adjusted to accommodate the appropriate format to yield optimal results.

We expanded our search to include randomized trials; however, our central focus was on finding prospective (and retrospective) cohort studies. The search strategy is provided below.

We validated our search strategy to ensure it retrieved a high proportion of studies. The search was repeated in the first week of May to ensure that any recent publications were included.

Reference lists of studies and reviews were searched to maximize study capture.

Additional Search Sources

In addition to the traditional literature search described, we also reviewed the COA and OTA conference abstract database from 2010 to 2020. A gray literature search was performed by searching with Google, Researchgate, Twitter, OpenGrey, Clinicaltrial.gov, WHO Library Database, PROSPERO, Open Science Framework, The National Research Register Archive (NRR), and MedNar. Four journals, Journal of Bone and Joint Surgery (JBJS), Bone and Joint Journal (BJJ), Clinical Orthopaedics and Related Research (CORR), and the Journal of Orthopaedic Trauma (JOT), were hand-searched from January 2015 to 2020. We also contacted several authors in the field to ensure the inclusion of any manuscripts in development.

Data Extraction

We extracted authors names, year and journal of publication, country of publication, center or centers where it was conducted, single versus multicenter status, type of data collection (prospective or retrospective), design, how the data was stored (i.e. charts, registry), missing data, year of origin, length of follow-up, blinding, cointervention, numbers and percent loss to follow-up, surgeon type who performed procedure if available (i.e. trainee or consultant), time that the procedure was performed, infection rate, deep infection rate (if available), superficial infection rate (if available), whether early or late infection (if available), infective organisms (if available), time to antibiotics, type of antibiotics administered, length of antibiotic administration, time from injury to hospital, whether the time measurements were made from the time from injury or admission (or both), irrigation in the emergency department (if available), type of irrigation solution, irrigation pressure, type of closure, timing of closure, dressing management, fixation type(s), other cointerventions, adverse surgical events (nonunion, malunion, fixation failure etc.), medical complications, and death. We also recorded age, gender, sociodemographic data, mechanism of injury, Gustilo type, bone or region injured or both, any reclassification of the injury at the time of surgery, risk factors such as smoking and alcohol use, as well as comorbidities such as diabetes.

We noted the statistical approach and recorded various measures to quantify the time to debridement. These included median and mean time to irrigation and debridement, event rate before and after specific reported cut points (i.e. 6 hours from injury), and any adjusted measures from regression or propensity analysis (i.e. odds ratio per hour delay in surgery). We paid

particular attention to the mean and/or median time to debridement for the early and delayed debridement groups (i.e. less than 6 or later than 6 hours). Assessment of the dispersion on either side of the cutoff is critical to evaluate the time differences between groups. With a sharp cutoff at 6 hours post-injury, the groups could be very similar or discrepant. The time to the hospital was similarly scrutinized, if available. If these were not reported, in several cases, we attempted to acquire that data from the authors and performed the analyses ourselves. We also developed a system for reporting antibiotics in open fracture care (see below).

Outcomes

We scrutinized the included studies for descriptions of any, superficial, and deep infections. If there was no description infection, this was automatically scored as high-risk for outcome assessment. We looked for details of superficial infections to indicate the infection was superficial to the fascia. For deep infections, we specifically looked for reports to describe it as being deep to the fascia and warranting reintervention. We also noted and recorded the reported method of outcome assessment, such as the Centers for Disease Control and Prevention (CDC) criteria^{1,2}.

ROBINS-I and GRADE Application

The ROBINS-I tool is specially designed for observational studies. It evaluates seven domains including 1) confounding, 2) selection bias, 3) misclassification of interventions, 4) cointervention (performance bias) or deviation(s) from intended intervention, 5) missing data and attrition bias, 6) detection bias, and 7) selective reporting bias. We added an eighth criterion of

whether the time origin was from injury or admission (i.e. injury time being the standard). If the study only recorded the time from admission to debridement, we considered this to have a high risk of bias because patients substantially delayed to the hospital can be treated expediently upon arrival, highly biasing the interpretation of the estimates. Disagreement was resolved by consensus or blinded referral of the question to a third author.

The GRADE system evaluates the level of confidence we have in the effect estimate based on six “downgrading” domains including 1) phase of investigation (i.e. phase 1), 2) study limitations, 3) inconsistency, 4) indirectness, 5) imprecision, and 6) publication bias; as well as two “upgrading” domains: 1) magnitude of the effect, and 2) presence of a biological gradient (i.e. dose-response). In general, the level of evidence is upgraded one level for a 2-fold increase in the estimate and two levels for a 5-fold increase. Phase 1 observational studies used to generate a hypothesis can, at best, report moderate-quality evidence. Higher-phase cohort studies that confirm the understanding between an underlying prognosticator and an outcome, of very high quality, can generate high-quality evidence if the estimates are sufficiently large.

Data Synthesis

If one of the cohorts (i.e. later than 6 hours) did not incur an event, we used a correction factor of 0.5 to facilitate analyses as per the Cochrane Handbook version 6.0^{3,4}.

We then conducted sensitivity analyses including 1) dichotomization at 6 hours post-injury (which included less than 5 hours for two studies)^{5,6}, 2) dichotomization at 12 hours (included less than 10 hours for one study)⁶, and 3) dichotomization at 24 hours. We then did separate analyses for Gustilo type III fractures to evaluate the effect of timing of debridement on infection risk. Gustilo type III analyses used a random effects inverse-variance method. For these analyses, we used every available cutpoint and conducted all possible comparisons (i.e. ≤ 6 hours versus >24 hours).

If heterogeneity was identified ($I^2 > 40\%$), the robustness of the results from our primary random-effects model was compared to the fixed-effect model. If the point estimate of the fixed-effect model was outside of the 95% confidence interval, we interpreted this to mean that the estimate was subject to substantial small-study bias. In those circumstances, we considered downgrading the evidence substantially for inconsistency⁷. Otherwise, the evidence was downgraded one level for ‘inconsistency’ with a threshold of $I^2 > 40\%$ ^{8,9}.

Study Search Results

As shown in Figure 1, the search of multiple databases yielded 26,857 potential references. Other sources provided 1,223 additional references. After removing duplicates, 15,167 titles remained. The titles and abstracts were screened for eligibility, and 4553 were excluded. The most frequent reasons for exclusion were that the abstracts indicated that the study evaluated fixation methods or antibiotic use only. There was mention of debridement in 10,614 abstracts, leading to full-text review. Other sources provided 1,223 additional references. After removing duplicates, 15,167 titles remained. The titles and abstracts were screened for eligibility, and 4553 were excluded.

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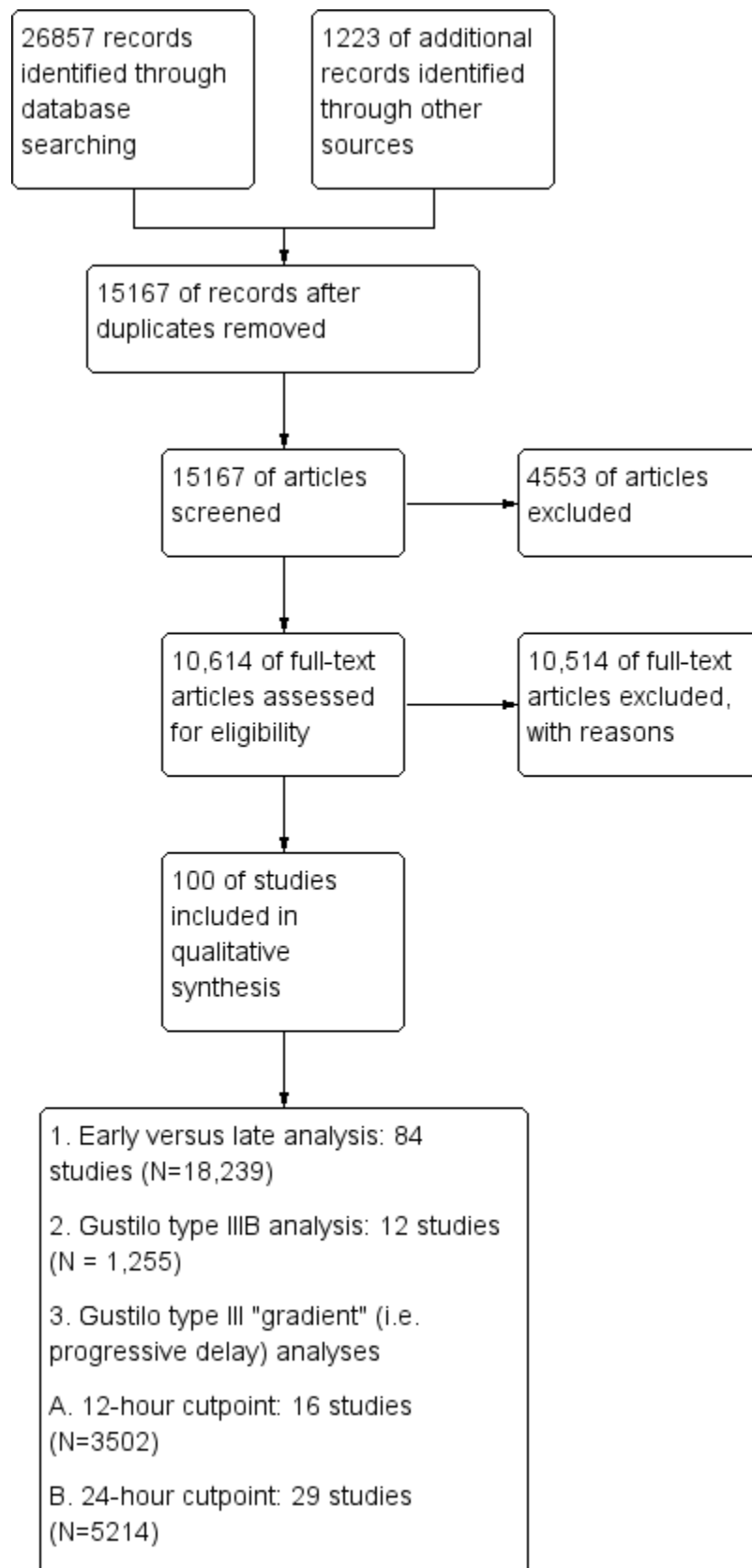


Figure 1: Study flow diagram. **Supplementary Details of Included Studies**

Of the 99 observational studies included, two were randomized trials¹⁰⁻¹² that reanalyzed their data (retrospective cohort study of a prospective RCT). The hundredth study was a randomized trial (i.e. actual RCT of early versus late debridement) that assigned patients to tibial fixation at less than six hours versus six to 24 hours postinjury.

A cutpoint of 8 hours was used in 7 studies (n=1277)¹³⁻¹⁹. Many studies provided data on multiple cutpoints. Those studies combined with ones that solely reported 12- and 24-hour cutpoints facilitated analysis of the 12-hour cutpoint in 23 studies (n=7763)^{6, 11, 16, 18-37}, and a 24-hour cutpoint in 28 studies (n=5413)^{16, 18, 19, 21, 26, 28, 29, 31-34, 37-53}. Fifty-nine studies enabled the extraction of either adjusted estimates or stratified event rates by Gustilo type^{5, 6, 14, 16-26, 28-30, 32-36, 44, 45, 47, 48, 51-81}.

In terms of studies that adjusted for confounding, fifteen studies that analyzed time to debridement as a continuous variable were included^{12, 15, 16, 19, 24, 28, 34, 36, 47, 62, 64, 65, 79, 82-84}. Fifteen reports performed adjustment for confounding and dichotomized groups at 6 or 8 hours or provided data that we independently analyzed with regression with a 6-hour cutpoint^{12, 17, 19, 24, 28, 34, 36, 59, 60, 62, 70, 79, 81, 83, 85, 86}. Five studies reported estimates on upper extremity fractures^{14, 17, 31, 34, 87}, one of which did not report an upper extremity event rate, but an adjusted estimate could be calculated¹⁷. Studies involving the tibia were common (25 studies, n=3346)^{5, 6, 18, 21, 22, 25, 33, 44, 53, 57, 61, 63-65, 68, 71, 73, 76, 77, 80, 81, 88-91}, as were manuscripts with Gustilo type III fractures (27 studies, n=2151)^{5, 6, 16, 20, 22, 23, 34, 48, 53, 54, 56-58, 61, 63, 64, 68, 69, 72, 73, 77, 80, 88, 91, 92}. The time origin was more commonly the moment of injury (39 studies, n=8924)^{5, 6, 11, 14-17, 20, 21, 24, 28-30, 33, 34, 44, 48, 53, 56, 58, 64-}

68, 71-73, 75, 79, 80, 87-95 than the time of admission (8 studies, n=3058)^{18, 31, 32, 47, 57, 61, 63, 77}. Twenty-five studies provided mean or median time to debridement for infected and non-infected individuals, seven of which only provided this data as a measure of treatment effect^{6, 10, 16, 23, 28, 34, 42, 44, 46, 48, 62, 64, 65, 70, 79, 82, 87, 90, 96-98}

Details of Reporting on Risk of Bias

Listed below is the full risk of bias summary for each study, except for data that was extracted from abstracts. In the event an abstract was available, authors were contacted. If we did not receive sufficient information, we did not formally evaluate the study for the risk of bias. However, they should be considered at high risk of bias for all intents and purposes. In five of the domains, 70% or more of the studies were at high risk of bias.

Confounding was the most common violation, as the central outcome aggregated all Gustilo types, which heavily confounds against a treatment effect of early intervention. We manually addressed some of the confounding by extracting the data by Gustilo type, or obtaining that data directly from the authors and generated adjusted (less biased) estimates from continuous data. These approaches substantially improved the accuracy and credibility of the estimates as well as mitigated the effect of outliers.

Methods of Assessment of Antibiotic Reporting

We also extracted the details of the antibiotic treatment reported in each study. We developed five criteria to evaluate the analysis and reporting concerning antibiotics. We asked if the following were adequately reported in the manuscript: 1) appropriate antibiotic choice, 2) time from injury to antibiotic delivery, 3) injury to antibiotic delivery adjusted for statistically, 4) duration of antibiotic administration, and 4) duration adjusted for statistically. We adapted the RevMan 5.3 Risk of Bias Tool to show the percentage of studies that fulfilled each criterion visually.

Findings on Antibiotic Treatment Reporting

Antibiotic administration is a critical part of reducing infection with a reported relative risk reduction of approximately 63% with an absolute risk reduction of 9.6%⁹⁹ (i.e. across all open fractures). Several studies have also demonstrated that the timing to antibiotic administration after injury is significantly correlated with surgical site infection^{55, 66, 90, 100}; however, there has been some conflicting data^{55, 90, 101}. Studies evaluating timing have generally had methodological issues. In addition, a recent study showed that a longer duration of antibiotic administration was protective in contaminated open fractures¹⁰².

To assess the quality of reporting of antibiotic treatment among studies, we evaluated each study according to five criteria. We identified that approximately 75% of studies reported that they

gave an appropriate antibiotic regimen or that a recognized protocol was followed (shown below). Sixty percent reported time from injury to antibiotics, and 40% reported duration. Less than 20% of reports statistically adjusted for time to administration (or injury to arrival to the hospital) or duration. In general, reporting has improved over the past five years, however, it remains inadequate. The lack of adjustment for this confounding source raises concerns. Our group will be issuing further guidance for researchers to build regression models to reduce confounding. We recommend that all studies report the antibiotics given for each Gustilo type, either in the text or appendix, or reference a recognized protocol. We also suggest reporting the level of compliance with any study or institutional protocol.

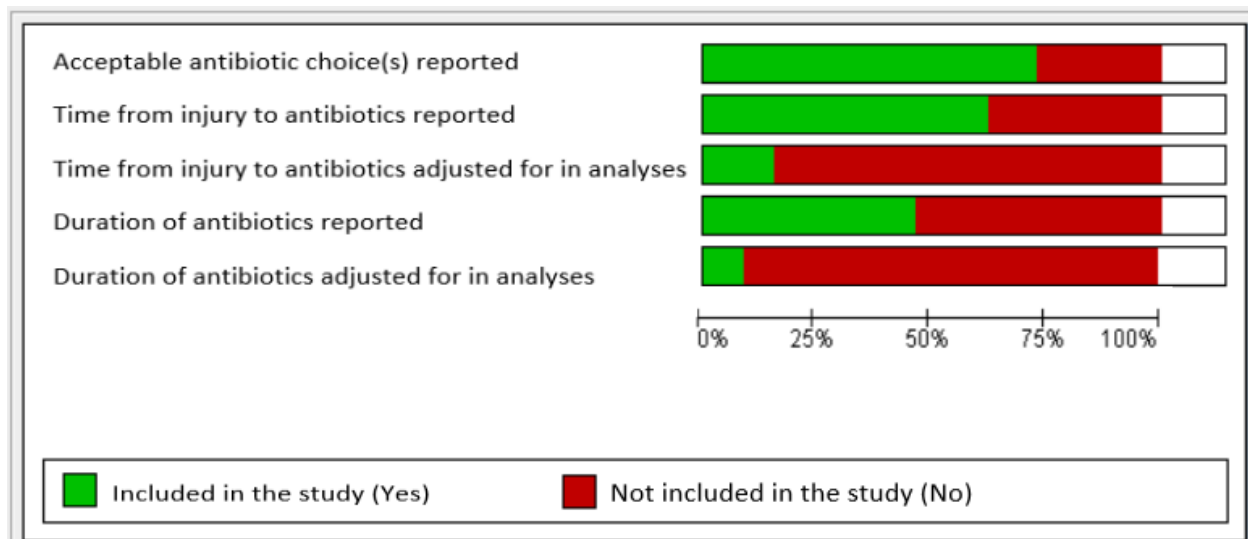


Figure 2: Reporting of antibiotic care in studies that evaluated the impact of time to debridement on the risk of infection.

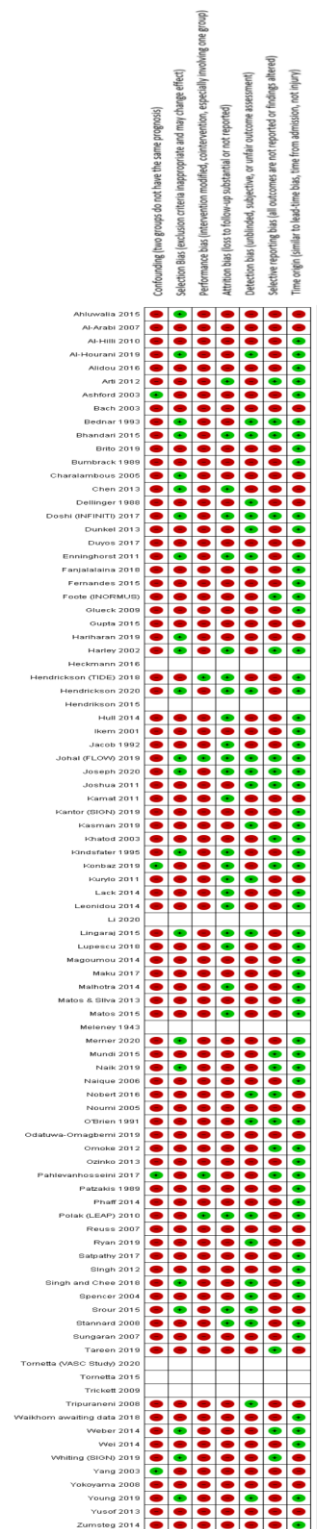


Figure 3a: Risk of bias summary for 97 studies found in the original search up to June 2020. Included conference abstracts were not formally evaluated for the risk of bias (represented by blank rows).

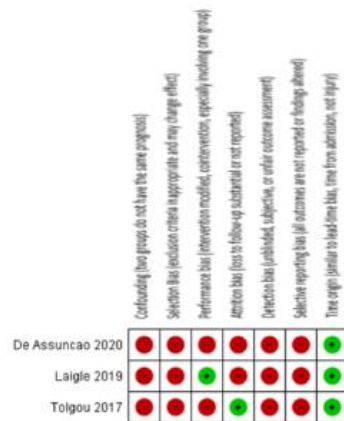


Figure 3b: Risk of bias summary for 3 studies found in the subsequent searches from June to September 2020.

Calculation of Relative Risks and Risk Differences (All Gustilo Types Analysis)

For the “early” versus “late” unstratified analysis (for Gustilo type) and IIIb tibial analysis (≤ 12 versus >12 -24 hours), we also calculated the relative risk (RR), in addition to the odds ratio (OR) using the method described by Zhang and Yo¹⁰³. For the IIIb tibial analysis we continued the analysis by calculating the risk difference between groups.

Relative Risk for Gustilo IIIb Tibia (Independent Analysis) and Early/Late Analyses

The relative risk for “late” (compared with “early”) was 1.22 (RR 1.22, 95% CI 1.09 to 1.37, $p < 0.001$). The OR was 1.29. Separate analyses with Gustilo IIIb open tibia fractures lead to a significant association between delay to debridement and infection (OR 1.46 95% CI to 1.89,

$p=0.004$, $I^2=23\%$, 12 studies, $n=1255$). Baseline risk is about 9.8% with treatment within 12 hours from our database. To make the relative risk conversion conservative, we used a higher baseline risk (i.e. we estimated baseline risk at 15.5%). The relative risk conversion was, therefore, 1.36 (95% CI 1.11 to 1.66). This leads to a risk difference at 12 to 24 hours versus less than 12 hours of 3.5% (95% CI 0.9% to 8.7%).

If we use the baseline risk from the GOLIATH database for debridement within 12 hours (i.e. ≤ 12 hours), it is 9.8%. The corresponding RR would then increase to 1.40 with Zhang and Yu conversion (RR 1.40, 95% CI 1.12 to 1.74). The risk difference at 12 to 24 hours versus less than 12 hours is now 3.9% (1.1% to 7.2%). This estimate is within 0.4% of alignment with the LEAP Study's risk difference in deep infection between those treated within 10 hours and those after 10 hours.

Time Origin Evaluation

Time from injury to debridement had a significant impact on infection risk (1.25, 95% CI 1.02 to 1.53, $p=0.05$, $I^2=19\%$, $n=39$, $n=8924$, very low quality) but studies that measured time from admission to debridement did not show an effect of delay (OR 1.00, 95% 0.65 to 1.53, $p=0.98$, $I^2=21\%$, 8 studies, $n=3058$, very low quality). Time from admission can have considerable bias analogous to “lead-time” bias, if the time to hospital is not considered in the analysis (i.e. long time to travel to the hospital, followed by early surgery after admission).

Deep Infection as an Outcome

It is worth noting that we removed superficial infections from the total count of infections where the descriptions provided were in sufficient detail to identify the event as a superficial wound infection.

Of the 84 studies included in the main analysis, 23 included acceptable definitions of deep infection and reported the deep infection event rates by group. We did not see a subgroup effect ($p=0.84$) with our primary outcome of infection. The effect estimate for “early” versus “late” among the 23 studies was similar in magnitude to the one reported in the text (OR 1.19, 95% CI 0.93 to 1.51, $p=0.15$, $I^2=16\%$, 23 studies, $n=7116$, very low quality).

Methodological and Analytical Issues with Previous Reviews

There were many issues with the current body of available reviews concerning time to debridement and surgical site infection. These include 1) an incomplete inclusion of clinical studies, especially international sources, 2) absent quality assessment that aids in the identification of sources of bias, 3) no identification of confounding, or an attempt to stratify by Gustilo type or acquire estimates of effect from regression, 4) incomplete review of experimental data, 5) no inclusion of unpublished data (positive studies have gone unpublished at a disproportionate rate), 6) analysis of metadata by only dichotomizing delay at 6 hours, and 7) the authors appeared to be prone to confirmation bias of no effect from study outset. We recognized that we were also subject to confirmation bias, initially entitling the study, ‘*Optimizing the*

Surgical Environmental for Thorough Debridement Reduces Infection Rates in Open Fracture

Care Not Time to Index Surgery A Systematic Review and Meta-analysis of Observational

Studies.' This further reveals the power of confirmation bias in this area of research.

Recommendations for Data Collection of Future Open Fracture Studies

We would emphasize the importance of the collection and reporting of the time to the hospital, time from injury to debridement, and time from admission to debridement. Depending on the purpose of the study, we recommend reporting all specifics about antibiotic choice, delivery times, and duration. Cointerventions such as negative pressure wound therapy, local antibiotics, and the specifics of interim and definitive fixation should be documented. Time and type of soft-tissue coverage are imperative, especially for studies with IIIB fractures. The cohorts should be stratified by Gustilo type with the stratified event rate. Regression analyses in observational studies are crucial to limit confounding. The power of the regression model should be considered. Rule of thumb is the model should have ten events (i.e. infections) for every variable in the model. Five events may be sufficient, but risks inflating type II error. As employed in this study, one can evaluate any time variable as a risk factor continuously or by using multiple cutpoints (i.e. ≤ 6 hours, $>6-12$ hours, >12 hours), or both (recommended). The median times are more useful than mean times; however, it is helpful to report both measures. Finally, if a confounder cannot be adjusted for due to limitations in the analysis or data collection, these should be identified and reported along with the hypothesized effect that confounding might have had on the estimate.

Table 1: Supplementary recommendations for future research concerning timing to debridement and other factors potentially associated with the adverse event rates in open fractures.

Factor	Application of Data
Time to hospital and/or time to antibiotic administration	Univariate and multivariate analyses
Time from injury to debridement	Univariate and multivariate analyses
Time from admission to debridement	Comparison with effect estimate from injury to debridement. Complex regression analyses. Stratify for time to hospital and evaluate if the association between time from admission to debridement changes (Novel idea).
Duration of antibiotics administration Relationship between time to closure and antibiotic administration	Univariate and multivariate analyses
Type of fixation strategy Definitive fixation at the time of debridement, temporary fixation with an exchange {i.e. temporary plate that is exchanged or removed at the time of nailing}, a provisional fixation	Evaluate for device and temporal fixation effects. Potentially stratify data by fixation strategy if it modifies the impact of delay on infection. Univariate and multivariate analyses.

that is maintained with definitive adjunct fixation (i.e. small fragment plate followed by definitive nailing)	
The timing of every source of fixation should be recorded.	Why record the timing of each fixation? For example, a model may produce no detrimental effect of provisional fixation (those that received it versus not). However, if we look at provisional fixation in situ >2 days, it may show a detrimental effect on infection rates. We can only perform this analysis if we have the times of the fixation. Considering running these analyses if you have a biologic/surgical rationale for doing it.
Time from definitive fixation to closure	Univariate and multivariate analyses
Resuscitation expediency: Arrived stable, hypotensive but rapid responder, hypotensive with prolonged resuscitation, severely hypotensive and very delayed resuscitation	Univariate and multivariate analyses. If effect modification exists, it may warrant data stratification.
NPWT usage and duration	Univariate and multivariate analyses

Gustilo type	Univariate and multivariate analyses adjustment or data stratification
Time from injury to closure	Univariate and multivariate analyses
Time from definitive fixation to closure	Comparison with the effect of time from injury to closure. Useful for adjustment when looking at the effect of other variables. Univariate and multivariate analyses.
If dichotomous outcomes are used (i.e. ≤ 12 and >12 hours from injury), report the means and median with standard deviations and interquartile ranges for BOTH groups. This way, we know if the groups are similar in the time they were treated, if they are appropriately spaced in the interval (i.e. mean 16.5 hours \pm 3.2 hours in the >12 -24 time interval), or hugely discrepant.	Univariate analysis for dichotomous outcomes. Multivariate analysis of dichotomous outcomes. Inform consideration of the interpretation of results based on findings of mean and medians between groups (i.e. are they too similar in times treated, appropriate, or too discrepant?). See the next point for more details to refine your analyses.
Outliers: Break down the event rate by time interval. Report the event rate for ≤ 12 hours versus >12 to 24 hours, >24 to 48 hours (consider >24 to 36 hours), and >48 to 72 hours, instead of reporting just >12 to 72	More precise time analyses. It can be used to assess the effect of progressive/gradient of time to bolster the strength of evidence. Outlier removal, if required, can be done in future meta-analyses because interval times

<p>hours, which limits analysis. Particularly, outliers cannot be identified if the <u>number of patients debrided</u> and <u>event rates (i.e. the number of infections)</u> are not reported for <u>each time interval</u> (importance: critical). If the study reports the mean and medians for these intervals, this provides additional information of where the majority of patients lie within the time interval.</p>	<p>have been reported (i.e. ≤ 6, 6-12, 12-24, 24-36, 36 to 48 hours etc.). If we want to look at ≤ 12 versus 12-24, if all of the time intervals are reported, this analysis is possible. Again, for each time interval ALL patients treated in that time interval must be reported AND the number of EVENTS (e.g. infections) in that time interval. For example, there were 64 patients debrided from 12-24 hours and six became infected.</p>
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Organizational Guidelines on Debridement

The American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP) updated guidelines, in joint partnership with the OTA, identifies the time to debridement as a quality indicator for trauma surgery¹⁰⁴. Their recommendation advocates for expedient debridement of open fracture wounds within 24 hours or sooner, depending on the musculoskeletal injury severity and the surgeon's clinical acumen. In addition, the National Institute of Health and Care Excellence (NICE) updated its guidelines in 2016, and the updated British Orthopaedic Association Standard for Trauma (BOAST4) standards are now available¹⁰⁵⁻¹⁰⁸. BOAST4 states open fractures should be debrided immediately for highly contaminated

wounds, within 12 hours for solitary high-energy open fractures, and within 24 hours for all other low-energy open fractures¹⁰⁸. Our findings support these guidelines.

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